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Prenatally Detected Hydronephrosis

The Incidence and Diagnostics of Vesicoureteral Reflux and Urinary Tract Infections

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ACADEMIC DISSERTATION

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To the memory of my father

Abstract

Background – The incidence of prenatal hydronephrosis is around one percent. In most of the cases, the finding remains insignificant for the child, but the variety of the abnormalities behind the finding is wide, including, for example, upper urinary tract obstruction, vesicoureteral reflux (VUR) and even difficult anomalies.

Aims of the study – Our target was to study the incidence of VUR and urinary tract infection (UTI) in children with prenatally detected hydronephrosis. We investigated the incidence VUR and UTI in children with simple hydronephrosis, hydroureter, duplex collecting system or ureterocele. Our aim was to detect the patients with the most significant risk of UTI based on the findings of the performed renal ultrasound (RUS) investigations and renal scintigraphies so that we could diminish the number of voiding cystourethrograms (VCUGs) performed in the future.

Patients and methods – By using electronical searching tools, we identified all the patients with diagnosis codes (ICD-10: Q60.0-Q64.9, N13.0 and N13.9) that suggested urinary tract disease or anomaly from our electronic patient record system. We included in the study patients who had an abnormal urinary tract ultrasound finding already during pregnancy and who had postnatally hydronephrosis (HN) and/or hydroureter, ureterocele or complicated duplex collecting system. All the information considering UTIs, imaging, laboratory results and clinical findings was explored manually. The incidence of UTI was compared to control patients who did not have abnormality that was supposed to expose to UTIs.

Results – Altogether 233 patients were included in the study: one hundred and thirty-five of them had HN without VUR, 24 patients had grade IV-V VUR, 12 patients had grade 1-3 VUR, 21 patients had non-refluxing hydroureter, 34 patients had complicated duplex collecting system, and seven patients had single system associated ureterocele. Duplex system was considered to be complicated when it was associated with either ureterocele, VUR or non-refluxing hydroureter. Thirty-two percent of the patients were girls. The risk of UTI was analyzed in two different studies. The first study concentrated on patients with simple abnormalities, while the patients with complicated duplex collecting system and single system associated ureterocele were analyzed in the latter study.
Despite the use of prophylactic antibiotics, the risk of UTI was significantly increased only in patients with grade IV-V VUR, ureterocele and VUR, ureterocele or duplex system associated non-refluxing hydroureter ($p = 0.001$, $p = 0.001$, $p = 0.012$ and 0.010 compared to the controls). The VCUG-associated risk of UTI was between two and three percent. The incidence of UTI was only 14% after mini-invasive perforation of ureterocele. Other bacteria than Escherichia coli predominated as pathogens in recurrent infections and in patients with complicated duplex collecting system or single system associated ureterocele. We also evaluated the sensitivity of renal ultrasound (RUS) examination in detecting grade IV-V VUR in patients with prenatally detected single system associated hydronephrosis or/and hydroureteronephrosis. According to multivariate analysis, only a visible ureter in RUS (OR 12.72; CI 5.33–32.04, $p < 0.001$) and shorter length of kidney in standard

deviation (SD) scale (SD 0 = 53 mm, 1 SD = 7 mm) (OR 2.67; CR 1.50–4.86, $p < 0.001$) predicted grade IV-V VUR in our material. Visible ureter in RUS predicted also UTIs in multivariate analysis (OR 5.93; CI 2.83–12.30, $p < 0.001$). On the basis on these findings, we created a three-grade risk scale where the renal units (RU) were scored based on the RUS findings. The incidence of grade IV-V VUR in RU was 2.9% in the low-risk group, 12.2% in the intermediate-risk group and 52.2% in the high-risk group. By using the scoring, 79% sensitivity and 82% specificity in detecting grade IV-V VUR was achieved. Additionally, we evaluated the usefulness of renal scintigraphy in diagnostics of VUR in our study. When a cut point of 44% differential renal function (DRF) in patient's worse kidney was used, 73% of the patients with grade IV-V VUR were detected. Only 21% of the patients without VUR and 22% of the patients with grade 1-3 VUR had the corresponding reduction of DRF. The results remained similar also when possible out-flow obstruction was taken into account.

Conclusions – The patients with prenatally detected HN and grade IV-V VUR, ureterocele or duplex collecting system in association with non-refluxing hydroureter had significantly increased risk of UTI despite the use of prophylactic antibiotics. According to our material, early mini-invasive perforation of the possible ureterocele should be considered. The risk of UTI associated with VCUG was about two to three percent. A visible distal ureter in RUS and reduced longitudinal diameter of kidney in SD scale and DRF of < 44% in patient's worse kidney in renal scintigraphy are predictive of grade IV-V VUR. By using a risk scoring based on the RUS findings, the amount of unnecessary VCUGs can be reduced significantly. According to our study, a top-down approach might be suitable also in case of ANH, and VCUGs could be further targeted on the patients with high risk of VUR in RUS and renal scintigraphy.

Lyhennelmä

Taustatietoa – Munuaisaltaan laajentumaa esiintyy raskauden aikana noin yhdellä prosentilla sikiöistä. Suurimmassa osassa tapauksia löydös jää lapsen kannalta merkityksettömäksi. Taustalla olevien poikkeavuuksien kirjo on kuitenkin laaja, käsittäen muun muassa ylempien virtsateiden virtausesteitä, vesikoureteraalista takaisinvirtausta (VUR) ja vaikeitakin rakennepoikkeavuuksia.

Tutkimuksen tavoitteet – Tavoitteenamme oli selvittää VUR:in ja virtsatieinfektioiden (VTI) esiintyvyyttä lapsilla, joilla oli raskauden aikana todettu munuaisaltaan laajentuma. Tarkastelimme VTI:n ja VUR:in esiintyvyyttä potilailla, joilla oli yksinkertainen munuaisaltaan tai virtsanjohtimen laajentuma, munuaisen kaksoisallassysteemi tai ureteroseele. Tarkoituksenamme oli lisäksi löytää virtsateiden ultraääni- (VTUÄ-) ja isotooppikuvausten pohjalta ne potilaat, joilla oli merkittävin virtsatieinfektioiden riski, ja pyrkiä jatkossa vähentämään tehtyjen miktiokystografiatutkimusten (MCG-tutkimusten) määrää.

Potilaat ja tutkimusmenetelmät – Aineistoamme varten haettiin sähköisestä potilastietojärjestelmästämme vuosilta 2003–2013 sähköisillä hakumenetelmillä kaikki potilaat, joiden diagnoosikoodi (ICD-10: Q60.0–Q64.9, N13.0 ja N13.9) viittasi virtsateiden sairauteen tai rakennepoikkeavuuteen. Tutkimuspotilaiksi hyväksyttiin ne potilaat, joilla munuaisten ultraäänilöydös oli ollut poikkeava jo raskausaikana ja joilla raskauden jälkeen todettiin munuaisaltaan ja/tai virtsanjohtimen laajentuma, ureteroseele tai komplisoitunut munuaisen kaksoisallassysteemi. Potilasasiakirjoista käytiin läpi käsin kaikki VTI:hin sekä kuvantamis-, laboratoriokoe- ja kliinisiin löydöksiin liittyvä tieto. VTI:n esiintyvyyttä eri potilasryhmillä verrattiin kontrollipotilaisiin, joilla ei ollut VTI:lle altistavaa rakennepoikkeavuutta.

Tutkimustulokset – Tutkimukseen hyväksyttiin yhteensä 233 potilaan tiedot. Näistä 135:llä oli munuaisaltaan laajentuma ilman todettua VUR:ia, 24:llä oli asteen IV-V ja 12:lla asteen 1-3 VUR, 21:llä laajentunut virtsanjohdin ilman VUR:ia, 34:llä komplisoitunut kaksoisallassysteemi ja 7 potilaalla yksinkertaiseen allassysteemiin liittyvä ureteroseele. Komplisoituneeksi kaksoisallassysteemiksi määriteltiin kaksoisallassysteemi, johon liittyi ureteroseele, VUR tai laajentunut virtsanjohdin ilman VUR:ia. Kolmekymmentäkaksi prosenttia potilaista oli tyttöjä. VTI:n riskiä analysoitiin kahdessa eri osatyössä: ensimmäisessä keskityttiin potilaisiin, joilla oli yksinkertainen rakennepoikkeavuus, kun taas jälkimmäisessä olivat mukana potilaat, joilla oli komplisoitunut kaksoisallassysteemi tai yksinkertaiseen allassysteemiin liittyvä ureteroseele.
VTI:n riski oli ennaltaehkäisevästä antibioottihoidosta huolimatta merkitsevästi kohonnut ainoastaan potilailla, joilla oli asteen IV-V VUR, ureteroseele ja VUR, ureteroseele tai kaksoisallassysteemiin liittyen laajentunut virtsanjohdin, johon ei liittynyt VUR:ia ($p = 0{,}001$, $p = 0{,}001$, $p = 0{,}012$ ja $0{,}010$ verrattuna kontrollipotilaisiin). MCG-tutkimukseen liittyi kahdesta kolmeen prosentin infektioriski. Ureteroseelen puhkaisun jälkeen infektioiden esiintyvyys oli ainoastaan 14 %. Muu bakteerit kuin Escherichia coli olivat

tavallisempia infektionaiheuttajia uusintainfektioissa ja potilailla, joilla oli komplisoitunut kaksoisallassysteemi tai yksinkertaiseen allassysteemiin liittyvä ureteroseele.
Tutkimuksessamme arvioitiin myös VTUÄ-tutkimuksen herkkyyttä havaita asteen IV-V VUR:ia potilailla, joilla oli raskausaikana todettu yksinkertaiseen allassysteemiin liittyvä munuaisaltaan tai/ja virtsanjohtimen laajentuma. Monimuuttuja-analyysin perusteella alaosistaan näkyvä virtsanjohdin (OR 12,72; CI 5,33–32,04, p < 0,001) ja suhteellisella asteikolla pienempi munuainen (SD 0 = 53 mm, 1 SD = 7 mm) (OR 2,67; CR 1,50–4,86, p < 0,001) olivat aineistossamme viitteellisiä asteen IV-V VUR:ille. VTUÄ:ssä näkyvä virtsanjohdin ennusti monimuuttuja-analyysin perusteella myös VTI:tä (OR 5,93; CI 2,83–12,30, p < 0,001). Näiden löydösten perusteella kehitettiin kolmiportainen riskiasteikko, jossa munuaiset pisteytettiin VTUÄ-löydösten pohjalta. Asteen IV-V VUR:ia esiintyi riskiasteikon matalan riskin ryhmässä 2.9 %:ssa, keskiriskin ryhmässä 12.2 %:ssa ja korkean riskin ryhmässä 52.2 %:ssa munuaisista. Riskipisteytyksellä saavutettiin 79 %:n herkkyys ja 82 %:n tarkkuus IV-V asteen VUR:in toteamiseksi.
Lisäksi työssämme arvioitiin isotooppikuvauksen käyttökelpoisuutta VUR:in diagnostiikassa. Käytettäessä raja-arvona alle 44 %:n suhteellista toimintaosuutta potilaan huonommassa munuaisessa löydettiin 73 % potilaista, joilla oli asteen IV-V VUR. Vastaava suhteellisen toimintaosuuden alenema todettiin ainoastaan 21 %:lla potilaista, joilla ei ollut VUR:ia, ja 22 %:lla potilaista, joilla oli 1-3 asteen VUR. Tulokset säilyivät samankaltaisina, kun mahdollinen virtauseste otettiin huomioon analysoinnissa.

Johtopäätökset – Potilailla, joilla on raskauden aikana todettu munuaisaltaan laajentuma ja asteen IV-V VUR, ureteroseele tai munuaisen kaksoisallassysteemi, johon liittyy laajentunut virtsanjohdin ilman VUR:ia, on merkittävästi kohonnut VTI-riski ennaltaehkäisevästä antibioottihoidosta huolimatta. Aineistomme perusteella mahdollisen ureteroseelen varhaista mini-invasiivista puhkaisua tulee harkita. MCG-tutkimukseen liittyi VTI-riski, joka oli noin kahdesta kolmeen prosenttia. Ultraäänikuvissa alaosistaan näkyvä virtsanjohdin ja munuaisen alentunut pituusmitta suhteellisella asteikolla sekä isotooppikuvauksessa havaittu alle 44 %:n suhteellinen toimintaosuus potilaan huonommassa munuaisessa viittaavat asteen IV-V VUR:iin. VTUÄ-löydösten pohjalta luodun riskipisteytyksen pohjalta voidaan merkittävästi vähentää tarpeettomien MCG-tutkimusten määrää. Myös raskaudenaikana todettuja munuaisaltaan laajentumia voisi tutkimustulostemme perusteella lähestyä aloittamalla tutkimukset VTUÄ:llä ja isotooppikuvauksella ja kohdistaa MCG:t näiden tutkimusten perusteella valituille potilaille, joilla asteen IV-V VUR:in riski on korkea.

Contents

List of original publications

This thesis is based on the following publications:

I Visuri S, Jahnukainen T, Taskinen S. Incidence of urinary tract infections in infants with antenatally diagnosed hydronephrosis – A retrospective single center study. J Pediatr Surg 2017; 52(9):1503-1506.

II Visuri S, Jahnukainen T, Taskinen S. Prenatal complicated duplex collecting system and ureterocele – Important risk factors for urinary tract infection. J Pediatr Surg 2018; 53(4):813-817.

III Visuri S, Kivisaari R, Jahnukainen T, Taskinen S. Postnatal imaging of prenatally detected hydronephrosis – When is voiding cystourethrogram necessary? Pediatr Nephrol 2018 Apr 7. doi: 10.1007/s00467-018-3938-y.

Visuri S, Kivisaari R, Jahnukainen T, Taskinen S. Correction to: Postnatal imaging of prenatally detected hydronephrosis – when is voiding cystourethrogram necessary? Pediatr Nephrol. 2018 Jun 15. doi: 10.1007/s00467-018-3986-3.

IV Visuri S, Jahnukainen T, Kivisaari R, Taskinen S. Reduced differential renal function in scintigraphy predicts high-grade vesicoureteral reflux in children with antenatal hydronephrosis. Acta Paediatr. 2018 Aug 16. doi: 10.1111/apa.14536.

The publications are referred to in the text by their Roman numerals and reprinted with the kind permission of their copyright holders. Some previously unpublished data are also presented.

Abbreviations

AHN	antenatal hydronephrosis
AUC	area under curve
CAP	continuous antibiotic prophylaxis
CI	confidence interval
DMSA	dimercaptosuccinic acid
DRF	differential renal function
DTPA	diethylenetriaminepentaacetic acid
GDNF	glial cell line-derived neurotrophic factor
HN	hydronephrosis
HNF1	hepatic nuclear factor 1
HOX	homeobox
HUN	hydroureteronephrosis
MAG3	mercaptoacetyltriglycenine
OR	odds ratio
PAX	paired box
PUO	pyeloureteral obstruction
ROC	receiver operating characteristic
RUS	renal ultrasonography
SD	standard deviation
UPJ	uretero-pelvic junction
US	ultrasonography
UTI	urinary tract infection
VCUG	voiding cystourethrography
VUR	vesicoureteral reflux
WT1	Wilms tumor 1

Introduction

Abnormalities of the urinary tract are one of the most common pathological findings in prenatally performed ultrasound examinations (Grandjean 1999). Dilated renal collection system is called hydronephrosis (HN), and when there is associated dilation of the ureter, the condition is called hydroureteronephrosis (HUN). Ureteral dilation can occur due to vesicoureteral reflux (VUR), obstruction or without either of them, so a dilated ureter can be a refluxing megaureter, a non-refluxing megaureter, or a non-refluxing-non-obstructive megaureter (Hodges 2010). Occasionally, an obstructive megaureter can be also refluxing (Weiss 1974). Great variation considering severity and pathology lies behind these abovementioned conditions (Mallik 2008). The clinical challenge thus lies in targeting further postnatal examinations: The unnecessary use of clinical resources and causing distress to the families should be minimized, without sacrificing the quality of diagnostics.

Urinary tract infections (UTIs) are one of the most common serious bacterial infections in children and febrile UTIs are associated with bacteremia in around 5.6% of cases (Megged 2017) The role of vesicoureteral reflux (VUR) behind UTIs has been a controversial topic in recent years (Venhola 2009). Thirty percent of the children with febrile UTI seem to have VUR (Sargent 2000, Lanning 1979). On the other hand, in a historical study by Kollermann and Ludwig, up to 60% of infants without any renal disease had at least some grade of VUR (Kollerman 1967). In 2010, Venhola et al. compared retrospectively the occurrence of VUR between children who had reliably diagnosed UTI and those whose diagnosis was non-UTI. In their study, the overall prevalence of VUR was 35% and it remained similar in the children without UTI (Venhola 2010). The risk of UTI associated with VUR also varies in different studies (Evans 2015, St Aubin 2013, Moore 2015). In previous studies, increased risk of UTI has also been linked to high-grade HN and HN with obstruction (Lee JH 2008).

Voiding cystourethrography (VCUG) has been a golden standard for detecting VUR (Committee on Quality Improvement, Subcommittee on Urinary Tract Infection 1999). While VUR exists in a minority of children with prenatal HN and renal ultrasound has seemed to be relatively insensitive method for detecting VUR, excessive amounts of unnecessary VCUGs have been performed (Zerin 1993, Gloor 2002). VCUG is one of the most common fluoroscopic studies that are performed on children, it exposes children to radiation, causes discomfort for the patients and families and leads to UTI in about one to two cases per a hundred performed studies (Smans 2008, Schneider 2001, Johnson 2017, Rachmiel 2005).

In this study, the risk of UTIs and VUR was evaluated in different groups of patients with prenatally detected HN who were admitted to our institution between the years 2003–2013. Complex urological anomalies, patients with early urinary diversion and syndromatic patients were excluded from this study. The main target of the study was to reduce the amount of unnecessary VCUGs by finding alternative ways with acceptable sensitivity and specificity to identify the patients with VUR and at high risk for UTI.

Review of the literature

1. Embryology

The development of the kidneys and the urinary tract is a complex process that starts at the beginning of the fourth gestational week and it can be disturbed in several phases, causing wide variation of functional and anatomical abnormalities. Initially, the nephrotomes, the nephrogenic tissue cords and the urogenital ridges are formed of the intermediate mesoderm. The development of the kidneys can be divided into three main phases: pronephros, mesonephros and metanephros, of which only the metanephros remains permanent. The development of the metanephros begins with the formation of the ureteric bud. Pax (paired box) and Hox (homeobox) genes, such as Pax2 and Hox11 paralogs, regulate the secretion of GDNF (Glial cell line-derived neurotrophic factor), which together with WT1 (Wilms tumor 1) are crucial factors in the formation of the ureteric bud. Mutations in several transcription factors (Pax2, WT1, HNF1 (hepatic nuclear factor 1) are known to cause urogenital malformations (Bouchard 2004, Sharma 2015).

The pronephros is represented in the cervical region by seven to ten solid cell groups. The indications of the pronephric system disappear by the end of the fourth week. The first excretory tubules of the mesonephros appear during the regression of the pronephric system. They form S-shaped loops and Bowman's capsule and acquire glomeruli at their medial extremities so that renal corpuscles are formed. The tubules lead to mesonephric (Wolffian) ducts. The mesonephros forms two ovoid organs, one on each side of the midline, and they are the lateral side of developing gonads. At the end of the second month the majority of the tubules have disappeared. In males, some of the caudal tubules and the mesonephric duct remain to participate in the formation of the genital system.

The metanephros, the permanent kidney, appears in the fifth week. Similarly as in the metanephric system, the excretory units of the metanephros develop from metanephric mesodermin. The collecting ducts are formed from the ureteric bud which penetrates the metanephric tissue and gives rise to the ureter, the renal pelvis and the major, and further, minor calyces. Meanwhile, during the fourth to the seventh week, the urinary bladder and urethra are divided from the cloaca.

The kidneys ascent to their final position from the pelvic region as the body curvature straightens and the lumbar and sacral regions grow in length. The onset of urine excretion occurs at the end of first trimester. After that, the fluid that is swallowed by the fetus is excreted back to amniotic fluid (Sadler 1995).

2 Prenatal ultrasonography

Intrauterine pregnancy can be detected by vaginal ultrasonography (US) as early as at the fifth gestational week when the amniotic sac can be identified (Bree 1989). The number of fetuses and about half of the major structural abnormalities can be detected by trans-abdominal and/or trans-vaginal scans at 11 to 14 weeks when also fetal nuchal translucency is measured (Fong 2004, Souka 2006). A malformation scan is performed between 18 and 22 gestational weeks for more accurate evaluation of fetal anatomy (McGormic 2017). In Finland, municipal healthcare is obliged to organize fetal US screenings at gestational weeks 10+0–13+6 and at gestational weeks 18+0–21+6 if the pregnant mother is willing (Valtioneuvoston asetus seulonnoista 339/2011).

Fetal kidneys and urinary bladder can be detected at US by 12–13 weeks gestation, but the volume of amniotic fluid can be assessed at the earliest after 16 weeks of gestation when the majority of the fluid is fetal urine (Fong 2004, Brohstein 1990, Brohstein 1994). Thus, a more precise evaluation of urinary tract abnormalities is performed at the malformation scan, or later on during the third trimester for patients with abnormal malformation scan (Andrés-Jensen 2016). If the fetus does not have even a single functioning kidney or has obstruction of ureters/urethra causing oligohydramnion, the consequences are hypoplastic lungs and limb anomalies (Ruano 2017, Oliveira 2000). This devastating situation, so-called Potter sequence, was first described in 1946 by Doctor Edith Potter (Potter 1946).

3 Prenatally detected hydronephrosis

The prenatal prevalence of HN is about one per hundred pregnancies, thus being one of the most frequent abnormalities detected in fetal ultrasound examinations (Ek 2007, de Grauw 2016). In most of the cases the finding turns out to be clinically insignificant, but the variety considering the abnormalities behind HN is wide and the clinical challenge lies in planning the postnatal examinations (Nguyen 2010).

Table 1. Classification of AHN due to renal pelvic antero-posterior diameter (APD) for mild, moderate and severe AHN (Mandell 1990, Nguyen 2010):

Degree of AHN	APD at second trimester, mm	APD at third trimester, mm
Mild	4 to < 7	7 to < 9
Moderate	7 to ≤ 10	9 to ≤ 15
Severe	> 10	> 15

AHN; Antenatal hydronephrosis

The risk of any postnatal pathology varies depending on the severity of AHN, being around 12% in mild ANH and 88% in severe AHN (Lee RS 2006). The most important predictor for worse postnatal outcome (as formerly mentioned) is oligohydramnion, which together

with AHN, enlarged bladder and "keyhole sign" representing dilated posterior urethra predict severe bladder outlet obstruction (McHugo 2001, Eckholdt 2004). Other predictors for postnatal pathology seem to be increased renal echogenity, poor cortico-medullary differentiation, parenchymal thinning, calyceal dilation and cysts of fetal kidney and urinoma (Chi 2006, Daïkha-Dahmane 1997, Stathopoulos 2010, Kleiner 1987).

In 2010, the Society of Fetal Urology (SFU) gave a consensus statement considering the evaluation of AHN. AHN presenting in third trimester should be postnatally controlled by renal ultrasound (RUS). In some cases where the anatomy is unclear further prenatal MRI should be considered. If the prenatal US finding represents bilateral moderate or severe ANH, or ANH is associated with bladder or urethral abnormalities or ureterocele, postnatal RUS is recommended to be performed by the age of three days. Otherwise, the first postnatal RUS should be done between two and four weeks of age (Nguyen 2010). According to the Finnish recommendation from 2006, the first postnatal US should be performed by the age of two days in case of ANH in patient's solitary kidney, bilateral AHN or big urinary bladder, which may be caused by posterior urethral valve. In milder cases, US should be performed at the age of one week (Ylinen 2006).

The most common postnatal finding following AHN is transient HN, followed by pyeloureteral obstruction (PUO) obstruction, VUR, ureteral dilation (with or without obstruction), ureteroceles and duplications (Lee RS 2006, Feldman 2001, Nguyen 2010). These findings will be discussed in later chapters.

4 Postnatal imaging of prenatal hydronephrosis

4.1. Ultrasonography of the urinary tract

4.1.1 General information

Being a non-invasive and safe investigation, ultrasonography (US) is the primary method for postnatal imaging of prenatal hydronephrosis. When US is performed during the first days after birth the severity of hydronephrosis might be underestimated because of a relative state of dehydration (Laing 1984). A single normal US within the first week after birth does not exclude obstruction. Thus, another US at the age of one month is recommended, especially if the patient gets symptoms such as abdominal pain and vomiting (Gatti 2001, Matsui 2008).

Renal size varies with the age and maturity of a neonate and is most commonly measured as upper-pole-to-lower-pole length (Blane 1985). A standard deviation (SD) scale is a simplified way to compare the results of longitudinal measurements against the average

results in the same age group (Rosenbaum 1984). Various parameters such as anatomical variations and echogenity of renal parenchyma, dilation of renal pelvis and ureter, ureterocele, volume of urinal bladder and thickness of urinal bladder wall can also be evaluated by US (Fernbach 1995, Vade 1987, Pauchard 2017, Bis 1990, Jequier 1987, Nguyen 2010).

4.1.2 Classifying hydronephrosis in renal ultrasonography

The antero-posterior diameter (APD) of the renal pelvis is a widely used method for evaluating renal pelvic dilation (Merquerian 2010). Recently, the cutoff of 10 mm in postnatal renal ultrasound (RUS) was recommended for the definition of renal pelvic dilation (Andrés-Jensen 2016). However, the children with renal APD between 7 and 10 mm may have significant nephrouropathies as well (Bouzada 2004, Ismail K 2004, Hálek 2010).

The Society of Fetal Urology (SFU) has created a classification which is more accurate for assessing HN as it also takes account calyceal dilation (Fernbach 1993).

Table 2. The Society for Fetal Urology Hydronephrosis Grading System (Fernbach 1993).

Ultrasound grade	Renal pelvis	Minor renal calyces	Renal parenchyma
0	Not imaged	Not imaged	Intact
1	Intrarenal thin stripe	Not imaged	Intact
2	Intrarenal board stripe Extrarenal	Not imaged Undilated	Intact
3	Extrarenal	Uniform dilation	Intact
4	Extrarenal	Uniform dilation	Reduced

4.2 Renal scintigraphy

Renal scintigraphies are important tools in the evaluation of renal functional parameters. The main practical challenges of the examination in children are the venipuncture and the need to keep them stable during the study (Mendichovszky 2017, Piepsz 2006). Due to the usage of intravenous radionuclides there is also some exposure to radiation associated with the examination (Arteaga 2017).

4.2.1 Dimercaptosuccinic acid scintigraphy

Tc-99m-Dimercaptosuccinic acid (DMSA) is cleared from circulation by tubular absorption and retained by the renal cortex (Mendichovszky 2017). DMSA scintigraphy is a standard method for detecting parenchymal defects in children (Mendichovszky 2017, Piepsz 2006). In top-down approach, DMSA scintigraphy is used to screen VUR in patients with febrile UTI, so that VCUG is performed only in patients whose scintigraphy finding is abnormal (Hansson 2004). DMSA scintigraphy can also be used for investigating renal morphology, for counting functioning renal cortical area and separate renal function and in diagnostics of acute pyelonephritis (Mendichovszky 2017, Piepsz 2006).

4.2.2 Diethylenetriaminepenta-acetic acid or mercaptoacetyltriglycenine scintigraphy

Tc-99m-Diethylenetriaminepentaacetic acid (DTPA) (which is dependent on glomerular filtration) and Tc-99m-mercaptoacetyltriglycenine (MAG3) (which instead is a tubular excretion tracer) are used for dynamic scintigraphy. In case of hydronephrosis the patients receive diuretics during the imaging. Dynamic scintigraphy is used for detecting obstruction in the upper urinary tract. It also presents separate renal function and can be used in diagnostics of reno-vascular hypertension and renal anomalies (Gordon I 2011 Mendichovszky 2017).

4.3 Voiding cystourethrography

Voiding cystourethrography (VCUG), in which the patient is catheterized and the bladder is filled with contrast agent, is a golden standard for evaluating the presence of VUR (Agrawalla et al. 2004, Committee on Quality Improvement, Subcommittee on Urinary Tract Infection 1999). The drawbacks of the study are discomfort to the patient, exposure to radiation and risk of UTI (Smans et al. 2008, Johnson et al 2017). VCUG is recommended at the age of two to four weeks if the RUS shows unilateral severe (SFU grade IV) HN in the first RUS examination or moderate (SFU grade III) HN which persists in the second RUS at the age of two to four weeks. If the initial RUS shows bilateral moderate or severe HN, VCUG is recommended during the first week after birth (Nguyen 2010).

5. Uretero-pelvic junction obstruction and transient hydronephrosis

The incidence of uretero-pelvic junction (UPJ) obstruction in children with AHN is about 10–30% compared to transient HN, which has an incidence of about 41–88 % (Nguyen 2010). Differentiation between UPJ obstruction and non-obstructive HN has remained

challenging despite the development of diagnostic methods, and the diversity concerning the incidence of these conditions in different studies reflects the difficulty of diagnostics and the different protocols of postnatal management of ANH (Nguyen 2010, Lee JN 2017, Piepsz 2009).

UPJ obstruction is more common in children with severe AHN, whereas the risk of obstruction is unlikely in patients with SFU grade ≤ 2 HN which can be followed without primary scintigraphy (Zee 2017, Nguyen 2010, Sairam 2001). The etiology of transient HN is somewhat unclear, but it may be associated with small dimensions or some natural folds and kinks in the uretero-pelvic junction (UPJ) (Nguyen 2010). While in most of the cases mild HN tends to resolve spontaneously, later worsening of HN is possible and the resolution of HN should be followed by US (Matsui 2008). The schedule of the US controls depends on the severity of dilation, and the interval during the first years remains somewhere between three months and one year (Nguyen 2010).

UPJ obstruction causes dilation to the renal collective system without either ureteral or bladder dilation. It can be bilateral (in up to 33% of the cases) and may be associated with other abnormalities, most frequently VUR, which occurs in about 8% of the cases with UPJ obstruction (Karnak 2008, Brown 1987). The typical clinical symptoms for UPJ obstruction are abdominal pain and vomiting (Rigas 2003). The indications for surgery have become stricter and according to prospective trials, about one fourth of the children with prenatally diagnosed UPJ obstruction require operative intervention (Palmer 1998, Arora 2015). Operative treatment is indicated when the functional scintigraphy shows obstruction in association with impaired or reducing renal function and/or progressive or giant HN (Arora 2015). Typical characteristics of transient HN are dilation of renal pelvis and normal cortical appearance in RUS with a descending profile and no deterioration of renal function in functional scintigraphy (Arora 2015, Mallik 2008).

6. Non-refluxing megaureter

Ureteral dilation, which is possible to detect in RUS, can occur due to grade III-V VUR, ureteral obstruction, a combination of VUR and obstruction or without either of them (Merlini 2005, Hodges 2010, Lebowitz 1985). Non-refluxing megaureter can be primary or secondary due to ureteral ectopia or ureterocele (Braga 2016). The secondary reasons are will be partially discussed later in this thesis. Non-refluxing megaureters seem to be associated with congenital ureteral muscle abnormalities and to increase with the occurrence of the AT2 A-1332G transition (Tokunaka 1984, Hohenfellner 1999).

The incidence of megaureters in patients with AHN is about 5–10%, it is more common on the left side, and males predominate in occurrence (Castagnetti 2012, Hodges 2010). About 72% of non-refluxing megaureters tend to resolve spontaneously while about 19–24% of them require operative intervention (McLellan 2002, Braga 2016). Poor spontaneous resolution and the need for surgery have been associated with larger primary diameter of

ureter (Calisti 2008, McLellan 2002, Braga 2016). In 2014, the British Association of Paediatric Urologists recommended surgical intervention for non-refluxing megaureter in case of symptoms such as febrile UTIs or pain. For asymptomatic patients, surgery is recommended if differential renal function is below 40% and the patient has massive or progressive hydronephrosis, or in case of a drop in differential function on serial renograms (Farruqia 2014). Later, in 2016, Drlík et al. found that the diagnosis of isolated low initial differential renal function is quite inaccurate and should not be an indication for surgery; the indications thus remain somewhat controversial (Drlík 2016).

7. Vesicoureteral reflux

Though vesicoureteral reflux (VUR) is known to be common among the young in many animal species, in people it is generally thought to be an abnormal finding. This perception is not clear as according to an early study, VUR might actually occur in as many as 60% of infants without any renal disease (Kollerman 1967). Usually the occurrence of VUR is assumed to be about one to two percent in healthy children and about 30–40 % in children with UTI, but the true occurrence in healthy children is unclear as it would not be ethical to perform VCUGs on healthy children without any urinary symptoms (Smellie 1975, Smellie 2001, Venhola 2009). VUR can occur primarily due to ureterovesical junction incompetence, which seems to be associated with a higher amount of CD68 positive macrophages and MMP-1 expression, or secondarily due to increased intravesical pressure (Oswald 2004, Nakai 2017).

Heikel and Parkkulainen published in 1966 their original work classification of VUR (Heikel 1966). Later on, in 1985, an international classification for VUR was published grading VUR into grades I-V (Lebowitz 1985).

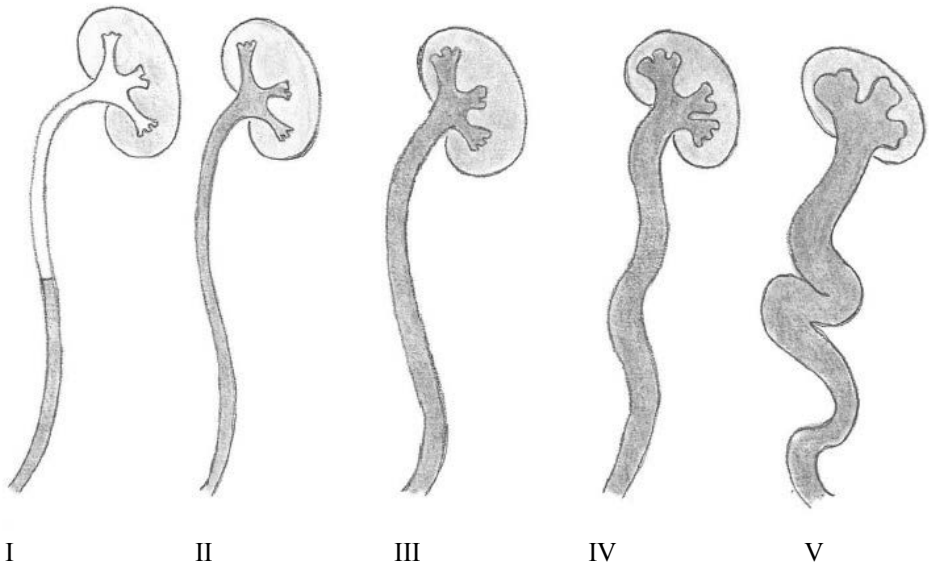


Figure 1. The international classification of VUR

It seems that grade I or II VUR is clinically insignificant and the morbidity, such as UTIs and renal parenchymal defects, is mostly associated with grade IV-V VUR (Mattoo 2016, Nordenström and Sjöström 2017, Venhola 2009). In boys with high-grade VUR, the renal parenchymal defects are often congenital, while in girls acquired scars seem to be more common (Nordenström and Sjöström 2017, Pirker 2006). In case of bilateral grade V VUR, spontaneous resolution is unlikely to occur (Nordenström and Holmdahl 2017). Due to the associated morbidity, operative interventions such as ureteral neoimplantation and mini-invasive para-ureteral anti-reflux injections have been used to treat VUR (Elder 1997, Nordenström and Holmdahl 2017). The high risk of UTI has led to recommendations on the usage of prophylactic antibiotics in patients with VUR (Elder 1997, Nguyen 2010).

In later years, the attitude towards VUR treatments has become more critical because even though the treatments can quite effectively eliminate VUR they seem to have rather limited influence on secondary outcomes such as renal scarring (Elder 1997, Venhola 2006, Nordeström and Sjöström 2017). The secondary outcomes with prophylactic antibiotics have turned out to be similar (Mattoo 2016). These findings support the idea that there is not a causal connection between renal scarring and primary VUR and that primary VUR, at least in boys, is rather a consequence than a cause of upper urinary tract pathology, and in mild cases, more or less a physiological phenomenon (Pirker 2006, Venhola 2009, Nordenström and Sjöström 2017). It seems that the nature of VUR is more gender-specific and that in boys, it is more a question of congenital dysplasia, which should be approached rather conservatively (Pirker 2006, Nordeström and Sjöström 2017).

8. Renal duplex collecting system

Ureteral duplication is the most common urological abnormality with about 2% incidence in early studies, and it is bilateral in about 20% of the cases (Privett 1976, Nordmark 1948, Fufezan 2013). In children with febrile UTI the incidence is about 8% and in children with AHN about 4% (Siomou 2006, Alladi 2000). Duplex collecting systems are more common in girls, and especially complete duplications are often associated with other abnormalities such as VUR, ureteroceles, ectopic ureters and poorly functioning pole moieties (Privett 1976, Bisset 1987, Siomou 2006). About 70% of the children with duplications and UTIs have associated abnormalities (Siomou 2006).

Renal duplications can usually be noticed in RUS, but in case of complicated duplications with associated anomalies DMSA scan, MAG3 renography, magnetic resonance urogram, VCUG and even cystoscopy and retrograde pyelography may be necessary for more accurate observation of the anatomy and renal function (Chan 2014, Fiqueroa 2014 Mendichovszky 2017, Chang 2016. Bansai 2014, Cezarino 2015).

While asymptomatic duplication is not an indication for surgery, recurrent UTIs, poorly functioning and hydronephrotic pole moieties, VUR, ectopic ureters and ureteroceles are the most common indications for operative treatment in children with renal duplications (Joyeux 2017, Castagnetti 2013). The usual operative interventions are heminephrectomies and endoscopic punctures of the ureteroceles, but also ureteral neoimplantations and ureteroureterostomies are performed in case of sufficient function of the consecutive pole moieties (Castagnetti 2013, Lapointe 1998, Grimsby 2014).

8.1 Complete duplication

In complete duplication there are two renal collecting systems with two ureters that lead to separate orifices (Fernbach 1997). The ureters can either drain into the bladder or ectopically. Ectopic ureters can drain into the bladder neck, urethra, vagina, vestibule, seminal vesicle, ejaculatory duct or prostatic urethra (Nordmark 1948, Terai 1995, Fernbach 1997). Ectopic drainage beneath the sphincter system is often diagnosed due to incontinence that appears in girls as continuous urinal dribbling, while ectopic ureter draining to the seminal tract can cause retrovesical cystic mass, perineal pain and voiding and ejaculatory symptoms (Chan 2014, Fernbach 1997, Terai 1995).

8.2 Partial duplication

In partial duplication (bifid system) there are two renal collective systems and two ureters as well, but the ureters unite before drainage into the bladder (Fernbach 1997). Whereas complete duplication is frequently associated with other urinary tract abnormalities, in the case of partial duplications the frequency of comorbidities is controversial and does not necessarily differ from single systems (Bisset 1987, Siomou 2006).

9 Ureterocele

The first description of ureterocele is from 1835, when Dr. Lechler found this structure on autopsy of a three-month-old boy and considered it to be a bladder duplicate (Lechler 1835). It is cystic dilation of the terminal ureter, bilateral in 10% of the cases and about four to seven times more common in females, with an incidence of about 0.2% (Uson 1961, Coplen 1995). In 80% of the cases, pediatric ureteroceles are associated with the upper pole of duplex collecting system and 60% have an ectopic orifice, while the ureteroceles that are diagnosed in adults are usually entirely intravesical and single system associated (Coplen 1995).

Ureterocele can typically be detected in RUS as a dilated ureter in association with a sonolucent round formation at the base of the bladder (Douglas 1995). The further investigation is VCUG, where it can be seen in the early phase of the imaging as a negative shadow surrounded by a rim of contrast, and in some further discussed cases it can even cause an outflow obstacle (Stephens 1958). After the radiological diagnosis is made and when the possible procedures are planned and performed, renal function can be defined by DMSA scan (Douglas 1995, Hodhod 2017). If the major finding in RUS is pelvic dilation instead of remarkable parenchymal loss, MAG3/DTPA renogram is chosen instead of DMSA (Mendichovszky 2017).

Ureteroceles are defined as intravesical and ectopic ureteroceles (Glassberg 1984). The precise classification was made by Dr. Douglas Stephens, who observed that obstruction is not an essential component for the formation of ureterocele (Stephens 1971). He classified ureteroceles into stenotic, sphincteric, sphincterostenotic, blind, ceco- and non-obstructive ureteroceles (Stephens 1958, Stephens 1971). Non-obstructed sphincteric ureteroceles decompress during sphincter relaxation, unlike cecoureteroceles, which get filled with urine during micturition, or sphincterostenotic ureteroceles; the last mentioned two types can thus cause urethral obstruction (Stephens 1958, Stephens 1971, Chalouhi 2017). In the worst case, ureteroceles can cause oligohydramnion and fetal pulmonary hypoplasia similarly to posterior urethral valve, which is why in recent years even fetoscopic interventions have been developed (Chalouhi 2017).

Small asymptomatic ureteroceles should be followed conservatively, but the symptomatic ones require operative interventions (Hodhod 2017). Transurethral incision of ureterocele seems to be a sufficient treatment, especially in the case of intravesical ureteroceles, for the majority of the patients (Hodhod 2017, Coplen 1995, Pfister 1998). Still, occasionally, especially with ectopic ureteroceles, either heminephrectomy, ureteral neoimplantation or ureterouretrostomy becomes necessary due to VUR or febrile UTIs (Pfister 1998, Hodhod 2017). The reoperation rate among patients with ectopic ureteroceles has varied from around 50% to up to 100% of the cases (Hodhod 2017, Shekarriz 1999, McLeod 2014).

A) **B)**

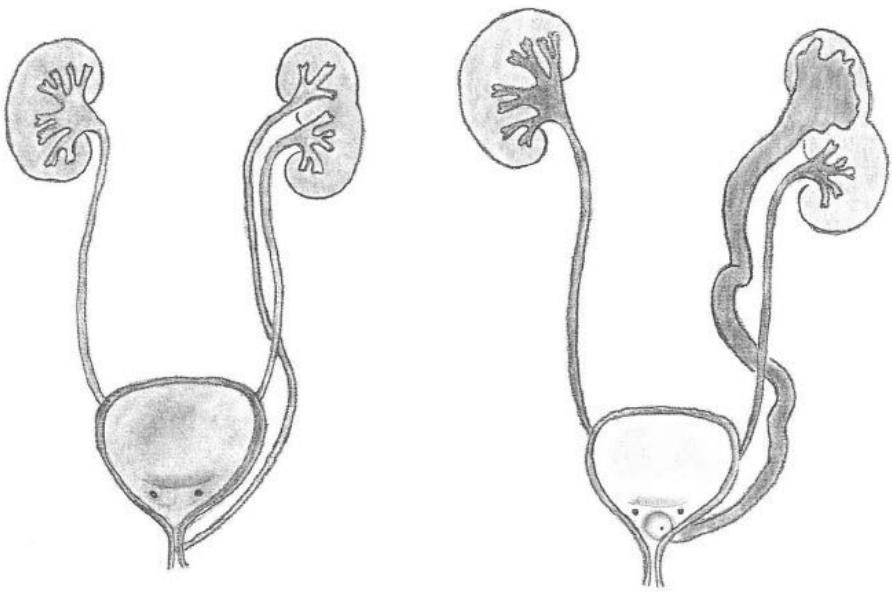


Figure 2.

A) A duplex collecting system and ectopic ureteral drainage to the urethra from the upper pole.

B) A duplex collecting system with upper pole hydroureteronephrosis. The ureter from the upper pole drains to the ureterocele located in the bladder neck.

10 Urinary tract infections

10.1 Epidemiology

Urinary tract infections (UTIs) are common bacterial infections in the pediatric population affecting about eight percent of girls and two percent of boys by the age of seven years (Hellström 1991). While girls have an about four-fold risk of UTI overall, in an early study by Winberg et al. boys predominated during the first six months of life (Winberg 1974). About 5.6% of febrile UTIs are associated with bacteremia (Megged et al. 2017).

Increased risk of UTI has previously been linked to high-grade VUR and ureteroceles (Conway PH 2007, Park 2013, Moriya 2015, Moriya 2017). In some studies, it has also been associated with upper urinary tract obstruction and higher grades of hydronephrosis, but these results remain controversial (Lee JH 2008, Braga 2017).

10.2 Diagnostics and complications

The most frequent bacteria causing UTI is E. coli, but non-E. coli-infections are typical in infants with urinary tract anomalies and they even seem to be predominant in UTI recurrences in children with VUR (Chakupurakal 2010, Jantunen ME 2001, Nordenström and Sjöström 2017).

The diagnosis of UTI is recommended to be based on sterile bladder puncture or transurethral catheterization in children who cannot yet provide clean voided urine sample (Committee on Quality Improvement, Subcommittee on Urinary Tract Infection 1999). While UTIs are frequently suspected in children with negative diagnosis, bladder puncture is not a suitable way to screen for UTIs (Kouri 1999). Thus, more comfortable ways such as urine bag and disposable nappies (which seem to be better than urine bags) are used (Ahmad 1991). If the screening sample is suggestive of UTI, the diagnosis should be confirmed by sterile bladder puncture or catheterization. Catheterization is more reliable than bag sample in diagnostics of UTI, but it is more easily contaminated than a puncture sample (Committee on Quality Improvement, Subcommittee on Urinary Tract Infection 1999). In the case of voided samples, two consecutive samples strengthen the diagnosis. Slide test is an appropriate method for screening UTIs, but urine samples that are suggestive of UTI when using a slide test should always be further cultivated (Committee on Quality Improvement, Subcommittee on Urinary Tract Infection 1999).

Any bacterial growth besides coagulase-negative staphylococci (in which case the limit is 20,000–30,000 colony forming units (CFU)) in a sample taken by bladder puncture is significant (Hoberman 1994). The limit of diagnostic growth varies somewhat depending

on the collection method of urine and the clinical condition of the patient and between different pathogens. Generally, the limit of significant growth of pathogen in clean voided sample is 10^5 CFU in milliliter (Committee on Quality Improvement, Subcommittee on Urinary Tract Infection 1999). However, even suprapubic aspiration is not fully accurate to diagnose UTI. It is shown that during the first year of life, around 1.4% of children have asymptomatic bacteriuria even in a suprapubically aspirated sample (Wettegren 1985).

Recurrent pyelonephritis may cause renal scarring especially in girls over one year of age (Mattoo 2016). During acute pyelonephritis, it is possible to see acute photon defects in DMSA, but the risk of permanent scars varies between 8 and 70 percent, so that the patients with the higher grades of VUR have the highest risk for scar formation (Lee YJ 2012). Acquired scars tend to be defined as focal cortical defects in DMSA, unlike congenital dysplasia, which appears as global cortical atrophy (Snoddgrass 2013). In some studies, recurrent pyelonephritis has also been described to cause hypertension and, in the worst case, renal failure (Jacobson SH 1989, Swerkersson 2007). The association between UTIs and renal scarring and further impaired renal function seems to be connected with VUR. Thus, the evidence showing the association between childhood UTIs and renal failure in structurally normal kidneys is poor (Swerkersson 2017, Salo 2011).

10.3 Antibiotic prophylaxis in children with AHN

Continuous antibiotic prophylaxis (CAP) is recommended for newborn patients with AHN when there has been: moderate or severe (SFU grade III-IV) HN, bladder or urethral abnormalities, dilated ureter or decreased amniotic fluid in prenatally performed US (Nquyen 2010).

CAP is usually carried out with either trimethoprim or nitrofurantoin. Nitrofurantoin might be more effective in preventing recurrent UTIs but the treatment is also more likely to be discontinued because of the (mainly gastrointestinal) side effects (Williams GJ 2006).

CAP seems to reduce the risk of UTIs in children with VUR, especially in children with grade IV-V VUR, in whom the risk seemed to decrease even more than 50% (Herz 2014, Wang 2015). CAP should be considered especially in females with higher grades of VUR as they have a greater risk for recurrent UTIs and acquired renal scarring (Nordenström and Sjöström 2017). On the other hand, CAP does not indisputably seem to prevent renal scarring (Wang 2015, Mattoo 2016). According to Conway et al., prophylactic antibiotics do not seem to be effective in preventing recurrent UTIs, either, and they lead to natural selection of resistant pathogens. Thus, the clinical benefits of CAP remain questionable (Conway PH 2007).

Aims of the study

Routine antenatal ultrasonography screenings have been performed for decades in developed countries. The most common abnormalities found in these antenatal US screenings are urinary tract anomalies, including hydronephrosis, cystic kidneys diseases, and renal hypoplasia or agenesia (Grandjean 1999, Gunn 1995). Antenatal US screening has significantly improved possibilities for the early diagnosis of severe urinary tract anomalies. However, it has also given rise to diagnostic dilemmas: Which of the findings are clinically significant? What type of imaging studies should be performed postnatally? Is postnatal follow-up necessary?

The aims of the study were:

I (Studies I and II) To evaluate the prevalence, etiology, and bacterial resistance of UTIs and the impact of operative interventions on UTI risk in children with prenatally detected HN classified as follows:

1. HN without other conditions
2. Non-refluxing HUN
3. Grade I-III VUR and IV-V VUR
4. Complicated duplex collecting systems
5. Single or duplex system associated ureteroceles

II (Studies III and IV) To evaluate the sensitivity and specificity of postnatal RUS examination and renal scintigraphy to predict grade IV-V VUR in infants with prenatally detected single collecting system associated HN or HUN without ureteroceles.

III (Studies I-IV) To explore possibilities to avoid unnecessary VCUGs in infants with prenatally detected urinary tract abnormalities.

Patients and controls

All patients with urinary tract abnormalities (ICD-10: Q60.0–Q64.9 and N13.0–N13.9) diagnosed between the years 2003 and 2013 were electronically searched from the Helsinki University Hospital's database. From these patients, we selected manually all neonates with prenatally detected non-refluxing HN (postnatal renal pelvic APD >7 mm), non-refluxing HUN (a visible distal ureter in RUS without VUR in VCUG), VUR, complicated duplex collecting systems and single and/or double system associated ureteroceles. Duplex collecting system was defined as complicated when it was associated with ureterocele, VUR, non-refluxing megaureter without ureterocele, or was combined with some of the other formerly mentioned abnormalities. The exclusion criteria were normal antenatal US but postnatally detected urinary tract abnormalities, bladder outlet obstructions, need for early urinary diversion, and urinary tract abnormalities in combination with other syndromes. None of the patients were circumcised. Patients with single and duplex collecting system were analyzed separately. However, patients with single collecting system associated ureteroceles were analyzed together with the patients with duplex collecting system. Patients with duplex collecting system were analyzed together with patients with ureteroceles. Thus, the patient population in this work can be divided into patients with simple and complex urinary tract abnormality (Table 3).

The age- and sex-matched control groups consisted of patients with suspected urinary tract abnormality in prenatal US and either normal postnatal renal US or a urinary tract abnormality supposedly not exposing to UTI. The abnormalities of the total 66 control patients were unilateral renal agenesis (n = 11), renal dysplasia or multicystic dysplasia (n = 37), single renal or ovarian cyst (n = 3), renal or adrenal cystic tumor (n = 2), ectopic kidney (n = 4) or adrenal hemorrhage (n = 1). RUS, VCUG, and renal scintigraphy were performed on all the control patients with dysplastic kidneys to exclude contralateral abnormality. The gender distribution was different between the two patient groups; thus the patients classified as having simple or complex urinary tract abnormality had partially different control patients.

Table 3. Total number and gender distribution of the different categories of the study population

	Diagnostic group	Boys	Girls	Total
Simple abnormality	*VUR gr 1–3, n (%)*	8 (67)	4 (33)	12
	VUR gr 4–5, n (%)	20 (83)	4 (17)	24
	Non-refluxing HUN, n (%)	16 (76)	5 (24)	21
	Non-refluxing HN, n (%)	100 (74)	35 (26)	135
Complex abnormality	*Complicated duplex collecting system*, n (%)*	9 (43)	13 (57)	21
	Single or duplex system associated ureterocele, n (%)	8 (40)	12 (60)	20
	All patients, n (%)	161 (69)	73 (31)	234
	All controls, n (%)	35 (53)	31 (47)	66

VUR, vesicoureteral reflux; HUN, hydroureteronephrosis; HN, hydronephrosis

* Duplex collecting systems with ureteroceles excluded

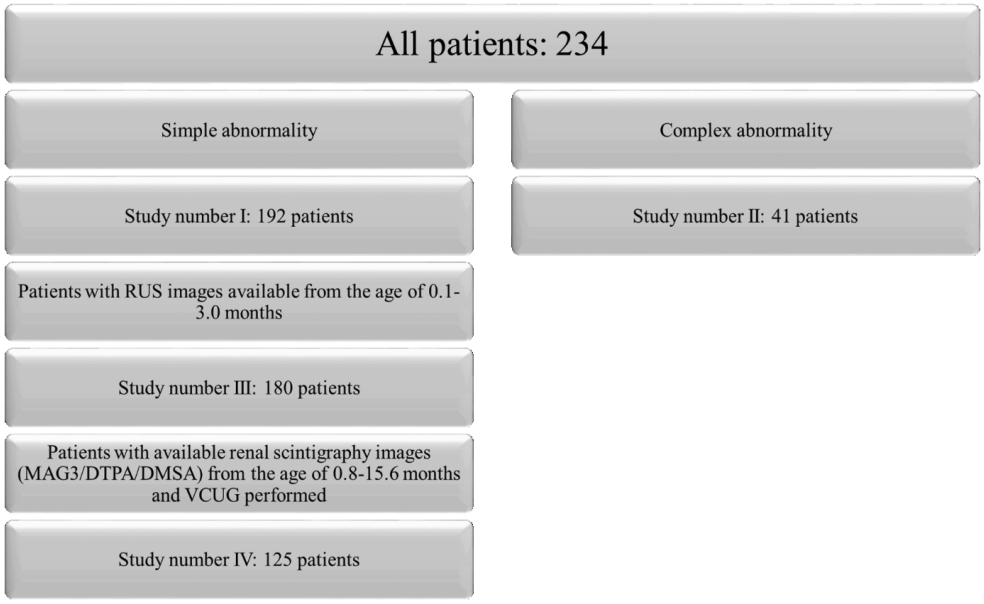


Figure 3. The patient distribution in the different studies

Methods

Data collection and study ethics

Information about age, gender, antimicrobial prophylaxis, results of the imaging studies and data about possible urological interventions were collected from patient records. Patient journals of the patients and controls were analyzed up to the latest visit to the pediatric surgical or pediatric outpatient clinic.

The study protocol had approval from the ethics committee of the Children's Hospital, Helsinki University Hospital and University of Helsinki.

Imaging studies and their interpretation

Renal US examination was performed in all 233 patients, renal scintigraphy (MAG3/DTPA/DMSA) in 202 (87%) patients, and voiding cystourethrography (VUCG) in 191 (82%) patients. DMSA scintigraphy was performed in case of reduced kidney size with minor (SFU grade 2) hydronephrosis in RUS, and MAG3/DTPA scintigraphy was performed in case of suspected obstructive uropathy and/or enlarged hydronephrotic kidney. Absence of elimination of the isotope in the MAG3/DTPA scintigraphy even after administration of furosemide was defined as obstruction.
VCUG was performed according to our standard protocol on patients with (1) visible ureter in RUS, (2) renal pelvic APD ≥ 10 mm, (3) HN in association with reduced size kidney, (4)

bilateral hydronephrosis, (5) duplex collecting system with renal pelvic or ureteral dilation and/or ureterocele. In a few cases, VCUG was performed based on individual indications after careful clinical consideration. According to our VCUG protocol, the bladder is filled with the contrast fluid until the patient micturates. The bladder is usually filled three times. VUR was classified according to the international reflux classification (Lebowitz 1985). In the case of bilateral VUR, the patient was categorized based on the higher grade of VUR. According to our protocol, all patients received antimicrobial prophylaxis with a therapeutic dose for three days starting on the morning of the examination day.

All RUS results and images obtained from patients with single collecting systems without ureteroceles at the age of 0.1–3.0 months were re-evaluated by an experienced pediatric radiologist. The SFU grading system of pediatric hydronephrosis was used for grading HN (Fernbach 1993). The renal parenchyma was evaluated from the mid-coronal section of the kidneys and classified as either normal or reduced. Dysplastic kidneys (multiple cysts or lack of corticomedullar differentiation in a non-hydronephrotic high-echogenic kidney) were excluded from the analysis.

In the final scoring in study III, the ureter was classified as visible or invisible and renal length was categorized into three categories based on the standard deviation scale: 1) > 53 mm (> 0 SD), 2) 46–53 mm (0–(-1) SD), and 3) < 46 mm (< (-1) SD). In studies III and IV, VUR was categorized into two categories: (1) grade I-III VUR and (2) grade IV-V VUR, based on the findings of the first study, where only the patients with grade IV-V VUR had increased risk of UTI.

Definition of UTI

Occurrence of UTI, bacterial etiology, and antimicrobial resistance profile were collected retrospectively from the laboratory database and patient journals.

The diagnosis of UTI was defined as significant pyuria (> 60 × 10E9/L) and 1) any bacterial growth in sterile suprapubic aspiration, 2) a bacterial count of ≥ 100,000 colony forming units per mL (CFU/mL) in voided samples (clean catch urine sample or in two consecutive bag urine samples), and 3) a bacterial count of ≥ 50,000 CFU/mL in a catheter sample.

Bacterial growth in bag urine sample was confirmed by either suprapubic aspiration or catheter sample, and in one case, by puncturing the pyonephros. In 17 (46%) patients, the diagnosis was based on two consecutive bag urine samples and in three (8%) patients, on one urine bag sample. However, all patients had clear clinical symptoms and findings suggesting UTI, including fever > 38.5ºC, significant bacterial growth of E. coli in urine, and significant pyuria (> 250–2063 × 10E9/L). In patients older than one month of age, pyelonephritis was defined as verified UTI together with fever (> 38.5°C) and/or CRP > 35 mg/L (Honkinen 2000). The pre- and postoperative UTIs were analyzed separately.

Indications of antimicrobial prophylaxis

Continuous antibiotic prophylaxis was initiated according to our protocol in patients with grade 3–5 VUR until continence, HN APD with ≥ 10 mm or non-refluxing hydroureter until the first year of life and in patients with complicated duplex collecting system or ureterocele until curative operation. In case of parental incompliance or refusal, antimicrobial prophylaxis was withdrawn.

Statistical analysis

Appearance of UTI was presented with Kaplan-Meyer curves, sample means were compared with Mann-Whitney test and categorical variables with Fisher's exact test. In study III, the risk of VUR and UTI was studied by univariate and multivariate logistic regression analysis and presented with ROC (receiver operating characteristic) curves. AUC (area under the curve) was also calculated.
Statistical analyses were done with SPSS statistical package (IBM SPSS statistics 22) and R (R package version 3.3.3) with the assistance of a biostatistician.

Results

General findings (Studies I and II)

The median follow-up time of the patients with simple urinary tract abnormality was 2.6 (0.3–11.2) years and of the patients with complex urinary tract abnormality 5.5 (1.7–12.2) years. The majority (67%) of all the first-time UTIs occurred during the first year of life. Thirty-six of the patients with UTI (86%) had pyelonephritis. The patients with grade IV-V VUR, ureterocele, and duplex system associated non-refluxing megaureter without either VUR or ureterocele had significantly increased risk for UTIs compared to the controls ($p < 0.001$, $p = 0.012$ and $p = 0.010$, respectively). There was no statistically significant difference in the occurrence of UTIs between males and females ($p = 0.243$) or in patients with simple or complex urinary tract abnormality ($p = 0.492$).

AHN and UTI (Studies I and II)

UTI occurrence before surgery in different patient groups compared to UTI occurrence in controls

Altogether thirty-seven (16%) patients and three (5%) controls experienced UTI before any surgical intervention (Table 4). Among the patients with simple urinary tract abnormality, only grade IV-V VUR was a significant risk factor for UTI. In these patients, the incidence of UTI was significantly increased when compared to the patients with HUN ($p < 0.001$), HN ($p < 0.001$), or to the control subjects ($p < 0.001$). In the patients with complex urinary tract abnormality, VUR without ureterocele did not increase statistically significantly ($p =$

0.209). Patients with ureterocele (p = 0.012) and non-refluxing megaureter (p = 0.010) had significantly more UTIs than the controls.

Table 4. Occurrence of UTIs in different patient groups and in the controls before any surgical intervention. P-value (Fisher's exact test) refers to difference between different patients groups and control group.

		Number of children	Patients with UTI (%)	p-value*
Simple abnormality	*VUR gr 1–3*	12	0 (0)	>0.999
	VUR gr 4–5	24	15 (63)	<0.001
	HUN	21	1 (5)	>0.999
	HN	135	8 (6)	0.726
	Controls (group I)	58	2 (3)	
Complex abnormality	*Duplex system and non-refluxing megaureter*	7	3 (43)	0.010
	Duplex system and VUR	14	2 (14)	0.209
	*Ureterocele**	13	4 (31)	0.012
	Single system	7	2 (29)	
	Double system	6	2 (33)	
	Ureterocele and VUR*	7	4 (57)	0.001
	Single system	1	1 (100)	
	Double system	6	3 (50)	
	Controls (group II)	66	3 (5)	

Abbreviations: UTI, urinary tract infection; VUR, vesicoureteral reflux

*Incidence of infections against the controls

** Single or double system

Causes of UTI, recurrence of UTI, and CAP

Twenty-one (63%) of the first-time infections were caused by E. coli while the majority (63%) of the recurrences were of non-E. coli etiology. All UTIs in the control subjects were caused by E. coli. E. coli caused a total 30 (68%) of 44 UTIs in the patients with simple abnormality and 13 of 28 (46%) UTIs in the patients with complex abnormality (p=0.087).

Fifty-four (75%) UTIs occurred before any operative interventions and 17 (31%) of them were UTI recurrences. Eleven patients (five with complex abnormality) had recurrent UTI, five patients had two recurrences, and one patient had three recurrences before operative treatment was performed.

Altogether 201 (86%) patients were on antimicrobial prophylaxis and 40 (20%) of them had complex abnormality. Forty-six patients (37 patients preoperatively and nine patients postoperatively) had altogether 72 UTIs. Forty (56%) of these UTIs occurred during CAP and fifteen (38%) of the UTIs that occurred during CAP were caused by E. coli.

VCUG-related infections

In our study population, a total of 310 VCUGs were performed. In nine cases (eight patients and one control), UTI occurred within one week after the examination, thus the occurrence of VCUG-related infections was 2.9%. Twelve percent of all infections in our material were caused by VCUG.

UTIs in patients with operative treatment

Seventy-eight (33%) patients underwent at least one operative intervention due to urogenital abnormality (Table 5). The median age at the first operation was 1.1 (0.1–5.7) years in patients with simple abnormality and 1.0 (range 0.1–3.1) years in patients with complex abnormality. Twenty-two (28%) of them had at least one UTI before the operation.

Table 5. The number of operative interventions and operated patients

	Type of surgical intervention	Girls	Boys
Simple abnormality	Endoscopic anti-reflux injection*	2	9
	Nephrectomy	0	2
	Pyeloplasty	10	16
	Ureteral catheterization**	0	4
	Ureteral neoimplantation	1	2
Complex abnormality	Endoscopic anti-reflux injection*	2	0
	Lower pole heminephrectomy	0	2
	Perforation of ureterocele	3	4
	Puncture pyelostomy	0	1
	Upper pole heminephrectomy	18	5
	Ureteral neoimplantation	4	2***
	Uretero-ureterostomy	1	0
	All interventions	41	47
	Operated patients	37	41

*Deflux®

**Catheter changed twice in one patient

***In one case ureteral remnant was dissected and ureterocele perforated as well

Despite successful surgery, 13 patients (seven with complex urinary tract abnormality) had altogether 18 UTIs after the operation. Nine (12%) of the operated patients (five with complex urinary tract abnormality) had their first UTI after the surgery was performed. It is of note that none of the patients with complex abnormality had more than one UTI after surgery and none of them was re-operated after the UTI. The risk of UTI after mini-invasive perforation of ureterocele was only 14%.

Parameters in RUS predicting VUR and UTI in patients with simple abnormality (Study III) RUS was performed at the median age of 1.3 (range 0.1–3.0) months in 180 patients. Twelve of the original 192 patients were excluded because the original images were not available

and could not be reanalyzed. VCUG was performed in 142 (75%) of the patients (278 RU) and only the patients with VCUG were included in the final VUR analysis.
Previous findings have suggested that the risk of UTI in patients with simple urinary tract abnormality is associated only with grade IV-V VUR. Therefore, VUR was categorized into two groups: grades IV-V (30 RU, 11%) and grade I-III (22 RU, 8%). An additional analysis was performed by pooling the patients with grade I-III VUR with the patients with non-refluxing HN.

The RUS findings suggesting the existence of gross VUR was analyzed. The risk of grade IV-V VUR was evaluated using the following parameters: 1) renal length, 2) renal pelvic APD, 3) SFU grade 0–2 versus grade 3–4, 4) visibility of distal ureter and 5) reduction of renal parenchyma. The predictive value of these parameters was analyzed using univariate analysis. Visible distal ureter was the most important risk factor predicting grade IV-V VUR (OR 13.57; CI 5.96–32.40, $p < 0.001$). Other significant risk factors for grade IV-V VUR were short renal length (OR 2.71; CI 1.48–5.25, $p = 0.002$), and SFU grade 3–4 (OR 2.52; CI 1.15–5.45, $p = 0.019$). Neither the pelvic diameter nor parenchymal thickness differed between the RU with grade IV-V and the RU with grade 0-3 VUR.

The parameters that were significantly associated with increased risk of grade IV-V VUR were further analyzed with multivariate analysis and the renal length was divided into three categories: 1) > 53 mm (> 0 SD), 2) 46–53 mm (0–(-1) SD), and 3) < 46 mm (< (-1) SD). In multivariate analysis, only a visible ureter and renal length significantly predicted VUR (OR 12.72; CI 5.33–32.04, $p < 0.001$ and OR 2.67; CI 1.50–4.86, $p < 0.001$, respectively).
Twenty-one of a total of 180 patients had UTI and VCUG was performed in all of them. The risk for UTI was analyzed with univariate analysis by using the above-mentioned parameters, but now only from the patients' worse RU, as in prediction of grade IV-V VUR. Only visible distal ureter in RUS turned out to be a significant risk factor for UTI (OR 4.93; CI 1.91–12.93, $p < 0.001$).

Scoring system predicting high-grade VUR (study III)

A scoring system was developed to predict the VUR risk. The scoring was based on the results of the multivariate analysis and the methodological guideline was adopted from the article published by Han et al. (Han 2016). The risk score took into account the visibility of ureter (yes/no) and renal length category (as described above). The patients were categorized into 1) low-, 2) intermediate- and 3) high-risk groups based on their scores. The incidence of grade IV-V VUR was 2.9% in the low-risk group, 12.2% in the intermediate-risk group, and 52.2% in the high-risk group (Table 6). Sensitivity (the true positive rate) and 1-specificity (the false positive rate) of the risk scoring to identify RU with grade IV-V VUR was analyzed by ROC (receiver operating characteristic) curve analysis. The AUC (area under curve) for the model was 0.817 (95% CI: 0.722–0.912) (Figure 4).

Table 6. The study population categorized into three risk groups for grade IV-V vesicoureteral reflux

Risk Group	Score*	VUR 0-3 (n=246)	VUR 4-5 (n=29)
Low, n (%)	0-1	201 (82)	6 (21)
Intermediate, n (%)	2-3	34 (14)	11 (38)
High, n (%)	4-5	11 (4)	12 (41)

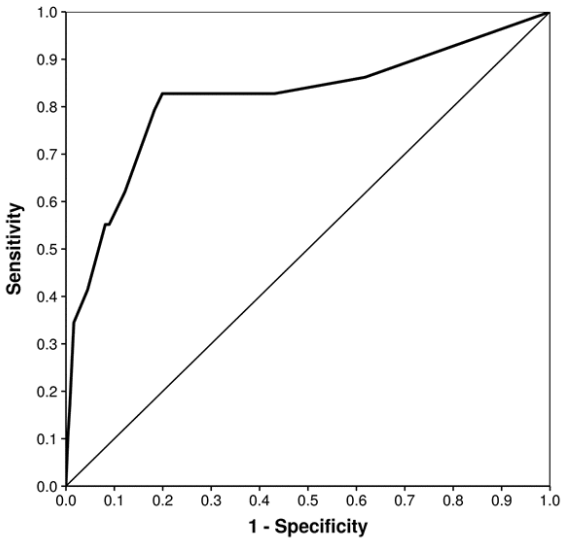
VUR; vesicoureteral reflux

*The risk score table is created by using a logistic multivariate regression model for the following parameters: 1) renal length and 2) ureteral visibility.

Variable	Beta	Categories	Points
Renal length	0.98	>53 mm**	0
		46 - 53 mm	1
		<46 mm	2
Ureteral visibility	2.54	Visible**	3
		Invisible	0

** The reference category

A)



B)

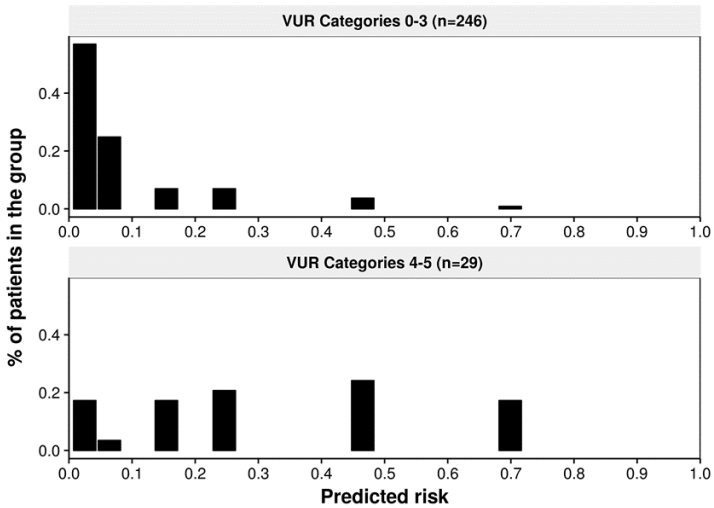


Figure 4. ROC (receiver operating characteristic) curve (A) and histograms (B) for the risk factors (visibility of ureter and reduced renal length in standard deviation scale in the renal ultrasonography imaging) for grade IV-V vesicoureteral reflux in patients with antenatally detected hydronephrosis. (Voiding cystourethrogram results were categorized as grade IV-V and grade 0–3.) In the ROC analysis, the area under curve for renal ultrasonography findings was 0.817 (95% CI: 0.722–0.912).

Renal scintigraphy in prediction of VUR and UTI in patients with simple urinary tract abnormality (Study IV)

One hundred and twenty-five patients were studied using both renal scintigraphy (MAG3/DTPA/DMSA) and VCUG at the median age of 1.4 (0.8–15.6) months. DMSA scan was performed in 28 (22%) and MAG3/DTPA renogram in 114 (91%) of the patients.

The patients with grade IV-V VUR had significantly lower partial function in their worse kidney than the patients without VUR (median 35 (IQR 20–45)% vs. 47 (IQR 44–49)%, $p < 0.001$). The difference between the patients with grade I-III VUR (median 47 (IQR 30–48)%) and patients without VUR was not statistically significant ($p = 0.181$). Eleven patients had obstruction in their worse kidney and six of them had < 44% of partial function in their worse kidney. Removal of those six patients from the analysis did not change the results.

The true positive rate (sensitivity) and the false positive rate (1-specificity) of the risk of identifying grade IV-V VUR were analyzed by ROC analysis. The AUC for the model was 0.790 (95% CI 0.672–0.909) (Figure 5). For the cut-point DRF below 44%, the sensitivity for detecting grade IV-V VUR was 73% and specificity was 79%. In addition, according to univariate analysis, DRF below 44% predicted significantly grade IV-V VUR (OR 9.818, 95% CI 3.436–28.055, $p < 0.001$).

Twenty (16%) patients (65% with grade IV-V VUR) experienced UTI at the median age of 7.8 (range 0–57.4) months before any surgical intervention. Five patients had UTI (at the median age of 1.1 (range 0–1.2) months) before the first scintigraphy was performed and they were excluded from the final analysis. The median function in the worse RU was 43% (IQR 34–46) in patients with UTI and 47% (IQR 42–49) in patients without UTIs ($p = 0.031$).

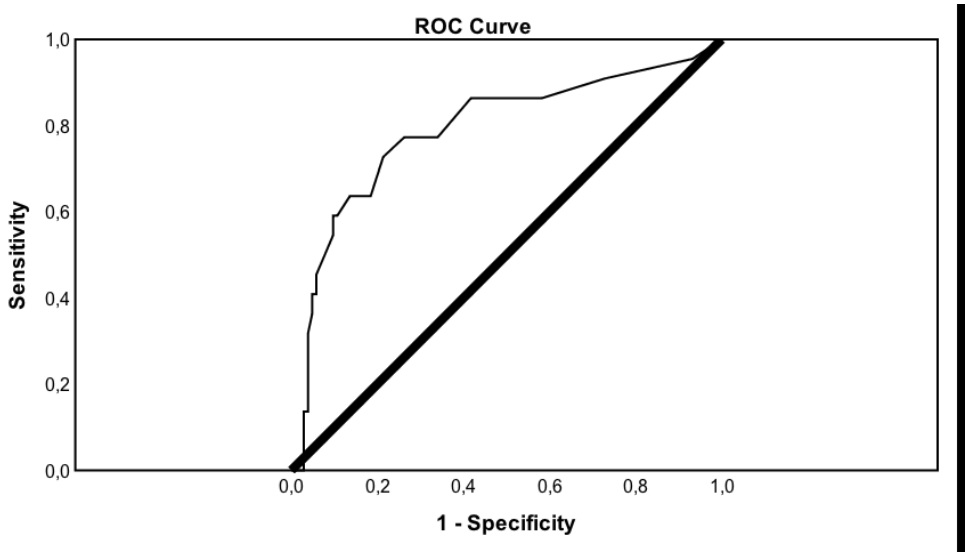


Figure 5. Receiver operating characteristic curve (ROC) for reduced differential renal function (DRF) as a risk factor for grade IV-V VUR. In the ROC analysis, the area under curve for 44% of DRF was 0.790 (95% CI 0.672–0.909).

Discussion

HN is a relatively common and clinically significant finding in prenatal ultrasonographies (Ek 2007, de Grauw 2016, Walsh 2007). It is found in approximately 1% of the fetuses. In about 15–21% of the cases, AHN is associated with VUR (Phan 2003, Brophy 2002). In most cases, AHN resolves spontaneously; however, there are no reliable methods available to distinguish patients who require postnatal imaging studies, treatment, and follow-up (Ek 2007).

Ultrasonography is indisputably the first postnatal investigation for a newborn infant with AHN. RUS is known to be a relatively insensitive method in detection of even high-grade VUR (Nguyen 2010, Zerin 1993, Gloor 2002). In a multidisciplinary consensus statement by Nguyen et al., the patients were classified into three categories based on the risk of postnatal uropathies according to the current literature. VCUG was only recommended for the high-risk patients who had peripheral calyceal dilation, abnormal renal parenchymal echo density, reduced parenchymal thickness, and abnormal ureter and bladder. In the low-risk groups, the decision for performing VCUG was recommended to be based on clinical consideration (Nguyen 2014).

In the present study, all RUS results and images were re-analyzed by an experienced pediatric radiologist. This analysis revealed that only 3% of the 30 RU with grade IV-V VUR met the abovementioned high-risk criteria (renal pelvic APD > 15 mm, peripheral

calyceal and ureteral dilation, and abnormal renal parenchyma). The current consensus statement gives suggestions as to which imaging studies should be performed in the case of the most severe types of AHN. Because a recommendation for milder AHN is lacking numerous unnecessary VCUGs are still performed.

Infants with AHN are almost 12 times more likely to be hospitalized due to pyelonephritis by the age of one year than infants without AHN (Walsh 2007). The increased incidence of UTI and UTI recurrences has been associated with high-grade VUR. The determination of high-grade VUR has varied depending on study protocol, as in some studies, high grade VUR includes grades IV-V while in others, grades III-IV are included in high grade VUR (Hannula 2012, Park 2013, Evans 2015, Nordenström and Sjöström 2017). In addition to VUR, also obstructive uropathy and severe hydronephrosis or non-refluxing hydronephrosis as well as female gender have been shown to increase the UTI risk (Lee JH 2008, Walsh 2007, Quirino 2012).

The current data suggest that AHN alone is not an independent risk factor for UTI. In patients with simple urinary tract abnormality, the risk of UTI was increased only in association with grade IV-V VUR, while low grade VUR (grade ≤ 3) did not increase the UTI risk. The present study could not confirm the association between UTI and female gender. This may be due to the young age of the study population and the dominance of male gender. Interestingly, infants with duplex collecting system in combination with non-refluxing hydroureter without ureterocele or VUR seemed to be at increased risk for UTI, while in patients with simple urinary tract abnormality the UTI risk was comparable to the control subjects. In patients with duplex collecting system, the impact of VUR remained controversial due to the small sample size. However, this study supports the previous findings showing that grade 1–2 VUR in association with duplex collecting system is clinically insignificant (Afshar 2005).

According to Chertin et al, UTI occurred before the operation in 20% of the patients who were selected for perforation of ureterocele at a median age of four months (Chertin 2005). The current study supports this finding as 40% of the patients with ureterocele in association with single or duplex collecting system had UTI before any surgery was performed.

In the present study, no statistical analyses were performed to evaluate the influence of surgery on UTI prevalence in different patient groups. It is still of note that the patients with complex abnormality had only single UTIs after the operative interventions and none of them needed further surgery due to the UTI. Especially after mini-invasive perforation of ureterocele, the rate of UTI was only 14%. Only few patients had UTIs after surgery, which is in line with the previous studies showing that febrile UTIs are uncommon in males after successful surgical decompression of the urinary tract (Castagnetti 2013).

Continuous antibiotic prophylaxis (CAP) has been suggested to reduce the risk of febrile UTIs in children with AHN, but also to increase the risk for antimicrobial resistance of the bacteria (Herz 2014, Wang 2015, Hoberman 2014, Braga 2013). In the present study, more

than half of the infections occurred during CAP and the majority of these break-through infections were caused by non-E. coli pathogens.

The present study showed that patients with simple urinary tract abnormality had increased risk for UTI only if they also had grade IV-V VUR. According to this finding, the majority of the VCUGs performed would be unnecessary. In addition, VCUG caused UTI in 2.9% of the children (patients and controls) despite antimicrobial prophylaxis. Therefore, it would be important to find methods to identify those patients who benefit from VCUG.
According to the previous studies, the following indicators are proven to be useful in VUR diagnostics: 1) uroepithelial thickening (appearing as hypoechoic rim within the renal pelvic wall), 2) central calyceal dilation, 3) parenchymal echogenicity and cortical thickness, 4) ureteral dilation, 5) bladder abnormalities and 6) kidney length (Gordon ZN 2016, Nguyen 2014, Muensterer 2002).

Based on the data from these previous reports, univariate analysis was performed in order to evaluate whether the risk for having grade IV-V VUR among patients with simple urinary tract abnormality can be predicted without VCUG. The following parameters were included: 1) renal length, 2) renal pelvic APD, 3) SFU grade 0–2 versus grade 3–4, 4) visibility of distal ureter and 5) reduction of renal parenchyma. Further analysis using multivariate analysis revealed that only ureteral visibility and renal length are able to predict grade IV-V VUR. Based on this finding, a scoring system taking into account ureteral visibility and renal length in RUS was created. The patients were categorized into two groups: those with grade 0–3 VUR and those with grade IV-V VUR. The scoring system was used to score these patients into low-, medium- and high-risk categories for grade IV-V VUR. The scoring was aimed to reach acceptable sensitivity and specificity to exclude the patients in the low-risk category from VCUG examinations, and according to ROC analysis, 79% sensitivity and 82% specificity was achieved. These same parameters were used to run univariate and multivariate analyses to test whether any of the parameters would be able to predict UTI risk. In this study population, only a visible ureter in RUS predicted UTIs. This result differs from an earlier study, which suggested that SFU grade IV-V HN increases the risk of UTI (Sencan 2014).

Renal scintigraphy has not been recommended for patients with AHN before RUS and VCUG have been performed (Nguyen 2010). Instead, in children with febrile UTIs, top-down approach was introduced already in 2004. According to this approach, VCUG is performed only if DMSA scan shows renal defects (Hansson 2004). To date, an increasing amount of evidence supporting the top-down approach has been published (Hansson 2004, Tsai 2012, Lee 2009, Tseng 2007).

One aim of this study was to evaluate whether top-down approach could be used in detection of grade IV-V VUR among children with simple AHN. MAG3/DTPA renogram was the most commonly used scintigraphy in this study population and therefore the results had to be interpreted. The results seemed promising as the patients with grade IV-V VUR (unlike the patients with grade I-III VUR) had significantly lower differential renal function in their

worse kidney than the patients without VUR. When a cut-point of < 44% in differential renal function in the patient's worse kidney in scintigraphy was used, 70% of the patients with grade IV-V were identified and approximately 80% of the unnecessary VCUGs could have been avoided. Reduced renal function also seemed to be associated with the risk for UTIs, which supported (Study 1) the earlier findings suggesting that AHN associated with high-grade VUR predisposes to UTI.

The main caveat of the current study is the relatively small study population. Therefore, only few sub-group analyses could be performed. The study population was not large enough to compare UTI risk in the presence of different types of urinary tract abnormalities or compare patients with febrile and afebrile UTI. Secondly, some patients had too short a follow-up time to draw any definite conclusion about the UTI risk. Thirdly, VCUG was performed in only 77% of the patients with simple urinary tract abnormality. It is therefore possible that some patients with VUR were missed. Fourthly, the majority of the patients received prophylactic antibiotics and one third of them were operated at relatively young age. This has most likely affected the UTI risk and in these cases the real UTI risk remains unclear. Fifthly, the urine samples were not collected in the same way. In addition to suprapubic (or pyonephros) aspiration, sterile catheterization, and free voided urine sample, also urine bag samples we accepted in the case of significant bacterial growth of a single uropathogen together with pyuria. Finally, due to the retrospective nature of the study, there were some limitations in the interpretation of imaging studies: 1) bladder fullness varied in the images, 2) bladder wall, renal cortical or uroepithelial thickness could not be measured, and 3) the most common types of scintigraphy were MAG3/DTPA renograms, which made the evaluation of renal parenchymal defects impossible.

This study has also several strengths: 1) the study population consisted of a well-defined cohort of AHN patients, with careful follow-up in a single center, 2) due to a centralized system, it is likely that all UTIs could be traced in this study population, 3) in all patients with UTI, the causing pathogen could be verified reliably, 4) the radiological imaging studies were performed in an experienced pediatric radiological unit, 5) the information about the medical history (including visits at the hospital, imaging studies and laboratory test results) was meticulously documented, and 6) the data of this study was manually explored and carefully read to ensure that there were no discrepancies between the clinical and laboratory findings considering UTIs.

Conclusions

I The risk of UTIs was significantly increased in patients with:

- Simple HN or HUN with grade IV-V VUR
- Single or duplex system associated ureterocele
- Duplex system associated non-refluxing megaureter

In case of ureterocele, early endoscopic perforation should be considered to prevent the UTIs.

II A visible ureter and reduced renal length in RUS and reduced partial function in patient's worse kidney in renal scintigraphy are significant predicting factors for high-grade VUR in patients with single system AHN.

III A significant proportion of unnecessary VCUGs can be avoided by using scoring based on visibility of ureter and renal length in RUS. Around 70% of patients with grade IV-V VUR can be identified by using top-down approach and cut point of < 44% of differential renal function in renal scintigraphy. Scintigraphy is perhaps not sufficiently sensitive to determine the need of VCUG, but it may function as a useful part of the diagnostic process.

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Lechaim – To Life!

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